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LISTING OF THE CLAIMS

1.   (Withdrawn) A method of identifying a compound that modulates nuclear receptor activity, the method comprising:

modeling a test compound that fits spatially into the nuclear receptor ligand binding domain using an atomic structural model of a portion of the estrogen receptor α ligand binding domain, wherein said atomic structural model comprises atomic coordinates of helix 12 of the ligand binding domain, and of a coactivator binding site, and further comprises atomic coordinates of a coactivator bound to the coactivator binding site; and screening said test compound in an assay characterized by binding of a test compound to the ligand binding domain, thereby identifying a test compound that modulates nuclear receptor activity.

2.   (Withdrawn) The method of Claim 1 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu 428, Gly 521, His524, Leu525 and Met528, and wherein said test compound interacts with at least one of said amino acid residues.

3.   (Withdrawn) The method of Claim 1 wherein the test compound is an agonist and nuclear receptor activity is measured by binding of a coactivator to the coactivator binding site.

4.   (Withdrawn) The method of Claim 1 wherein the test compound is an antagonist and nuclear receptor activity is measured by a change in position of helix 12 so that helix 12 contacts the coactivator binding site thereby inhibiting coactivator binding.

5.   (Withdrawn) The method of Claim 1 wherein the test compound is an antagonist and nuclear receptor activity is measured by blocking of coactivator binding.

6.   (Withdrawn) The method of Claim 1 wherein said screening is in vitro.

7.   (Withdrawn) The method of Claim 6 wherein said screening is high throughput
screening.

8.   (Withdrawn) The method of Claim 1 wherein said test compound is from a library of
compounds.

9.   (Withdrawn) The method of Claim 1 wherein said test compound is a small organic
molecule, a peptide, or a peptidomimetic.

10.   (Withdrawn) The method of Claim 1 wherein the modeling comprises providing the
atomic coordinates of the portion of the estrogen receptor α ligand binding domain to a
computerized modeling system.

11.   (Withdrawn) The method of Claim 1 wherein said nuclear receptor is selected from the
group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid
receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome
receptors and vitamin D receptors.

12.   (Withdrawn) The method of Claim 11 wherein said nuclear receptor is an estrogen
receptor.

13.   (Withdrawn) The method of Claim 12 wherein said estrogen receptor is the estrogen
receptor α.

14.   (Withdrawn) A method of identifying a compound that modulates ligand binding to a
nuclear receptor, the method comprising:

modeling a test compound that fits spatially into the nuclear receptor ligand binding

domain using an atomic structural model of a portion of the estrogen receptor α ligand binding

domain, wherein the atomic structural model comprises atomic coordinates of helix 12 of the

ligand binding domain, and of a coactivator binding site, and further comprises atomic

coordinates of a coactivator bound to the coactivator binding site; and

screening said test compound in an assay characterized by binding of the test compound to the

ligand binding domain, thereby identifying a test compound that modulates ligand binding to

said nuclear receptor.

15.   (Withdrawn) The method of Claim 14 wherein the atomic structural model additionally

comprises coordinates of amino acid residues that correspond to human estrogen receptor α

residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421,

Leu 428, Gly 521, His524, Leu525 and Met528, and wherein said test compound interacts with

at least one of said amino acid residues.

16.   (Withdrawn) The method of Claim 14 wherein said nuclear receptor is selected from the

group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid

receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome

receptors and vitamin D receptors.

17.   (Withdrawn) The method of Claim 16 wherein said nuclear receptor is an estrogen

receptor.

18.   (Withdrawn) The method of Claim 17 wherein said estrogen receptor is the estrogen

receptor α.

19.   (Withdrawn) The method of Claim 14 wherein said screening is in vitro.

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20. (Withdrawn) The method of Claim 19 wherein said screening is high throughput screening.

21. (Withdrawn) The method of Claim 14 wherein said test compound is from a library of compounds.

22. (Withdrawn) The method of Claim 14 wherein said test compound is an agonist of ligand binding that facilitates binding of a coactivator to the coactivator binding site.

23. (Withdrawn) The method of Claim 14 wherein said test compound is a small organic molecule, a peptide, or a peptidomimetic.

24. (Withdrawn) A method for identifying an agonist of ligand binding to an estrogen receptor the method comprising:

modeling a test compound which fits spatially into an atomic structural model of the estrogen receptor α ligand binding domain, wherein the atomic structural model comprises atomic coordinates of helix 12 of the ligand binding domain, and of a coactivator binding site, and further comprises atomic coordinates of a coactivator bound to the coactivator binding site; and screening in an assay for estrogen receptor activity a compound which increases the activity of the estrogen receptor by binding the ligand binding domain of the estrogen receptor, thereby identifying an agonist of ligand binding.

25. (Withdrawn) The method of Claim 24 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528, and wherein said test compound interacts with at least one of said amino acid residues.

26 – 28. (Cancelled).

29.   (Withdrawn) A method of modulating nuclear receptor activity in a mammal by
administering to a mammal in need thereof a sufficient amount of a compound that fits spatially
and preferentially into a ligand binding domain of the nuclear receptor, wherein said compound
is designed by a computational method that involves fitting an atomic model of the compound
into an atomic structural model of the ligand binding domain of the estrogen receptor that
comprises atomic coordinates of helix 12 of the ligand binding domain, and of a coactivator
binding site, and further comprises atomic coordinates of a coactivator bound to the coactivator
binding site, so that the molecule interacts with at least one amino acid residue corresponding to
residues of human estrogen receptor α Met343, Leu346, Ala350, Glu353, Leu384, Leu387,
Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528.

30.   (Withdrawn) The method of Claim 29 wherein the test compound is an antagonist that
causes a change in position of helix 12 so that helix 12 contacts the coactivator binding site
thereby inhibiting coactivator binding.

31.   (Withdrawn) The method of Claim 29 wherein said nuclear receptor is selected from the
group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid
receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome
receptors and vitamin D receptors.

32.   (Withdrawn) The method of Claim 31 wherein said nuclear receptor is an estrogen
receptor.

33.   (Withdrawn) The method of Claim 32 wherein said estrogen receptor is the estrogen
receptor α.

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34. (Withdrawn) A machine-readable data storage medium encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecular complex, wherein the data comprises coordinates of: a portion of an estrogen receptor ligand binding domain, including helix 12 of the ligand binding domain; a coactivator binding site; and a compound bound to the estrogen receptor coactivator binding site.

35. (Withdrawn) The machine-readable data storage medium of Claim 34 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528.

36 – 38. (Cancelled)

39. (Withdrawn) The machine-readable data storage medium of Claim 34 wherein said molecular complex is defined by the set of structure coordinates depicted in Appendix 1, or a homologue of said molecular complex, said homologue having a root mean square deviation from the coordinates of the backbone atoms of said ligand binding domain of not more than 1.5Å.

40. (Withdrawn) A machine-readable data storage medium comprising a data storage material encoded with a first set of machine readable data which, when combined with a second set of machine readable data, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data, wherein: said first set of data comprises a Fourier transform of at least a portion of the structural coordinates selected from the group consisting of coordinates depicted in Appendix 1 or Appendix 2; and said second set of data comprises an X-ray diffraction pattern of a molecule or molecular complex.

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41.   (Withdrawn) The machine-readable data storage medium of Claim 40 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.

42.   (Withdrawn) The machine-readable data storage medium of Claim 41 wherein said nuclear receptor is an estrogen receptor.

43.   (Withdrawn) The machine-readable data storage medium of Claim 42 wherein said estrogen receptor is the estrogen receptor α.

44.   (Currently amended) A cocrystal comprising: a portion of consisting of: an estrogen receptor α ligand binding domain; an agonist bound to the ligand binding domain, wherein the agonist is selected from the group consisting of: diethylstilbestrol; moxestrol; mesohexestrol; coumestrol; Δ9-THC; o,p-DDT; zearalenone; and kepone; and a molecule bound to a coactivator binding site of the estrogen receptor, wherein the molecule is GRIP1 or a peptide fragment thereof, wherein the peptide fragment comprises a NR-box amino acid sequence.

45.   (Cancelled)

46.   (Currently amended) The cocrystal of Claim [[45]] 44 wherein said estrogen receptor α is human.

47.   (Cancelled)

48.   (Cancelled)

49.   (Withdrawn) A cocrystal comprising: a portion of an estrogen receptor ligand binding domain and an antagonist bound to the ligand binding domain, wherein said cocrystal diffracts with at least 1.9Å resolution.

50.   (Previously presented) The cocrystal of Claim 44 wherein said cocrystal diffracts with at least 2.03 Å resolution.

51.   (Withdrawn) The cocrystal of Claim 49 wherein said estrogen receptor is human.

52.   (Withdrawn) A computational method of designing a nuclear receptor ligand, comprising:

        fitting an atomic model of the ligand into an atomic structural model of the ligand
        binding domain of the estrogen receptor, wherein the atomic structural model comprises
        atomic coordinates of helix 12 of the ligand binding domain, and of a coactivator binding
        site, and further comprises atomic coordinates of a coactivator bound to the coactivator
        binding site; and
        carrying out a chemical modification of a first chemical moiety of said ligand that
        interacts with the ligand binding domain, to produce a second chemical moiety.

53.   (Withdrawn) The method of Claim 52 wherein the atomic structural model additionally comprises coordinates of at least one amino acid residue that corresponds to human estrogen receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528, and wherein said first chemical moiety interacts with at least one of said amino acid residues.

54.   (Withdrawn) The method of Claim 52 further comprising determining a change in interaction between said interacting amino acid and said ligand after the chemical modification of said first chemical moiety.

55.   (Withdrawn) The method of Claim 54 wherein said chemical modification enhances an interaction selected from the group consisting of: hydrogen bonding interaction, charge interaction, hydrophobic interaction, van der Waals interaction or dipole interaction between said second chemical moiety and one of said amino acid residues compared to said first chemical moiety.

56.   (Withdrawn) The method of Claim 54 wherein said chemical modification reduces an interaction selected from the group consisting of: hydrogen bonding interaction, charge interaction, hydrophobic interaction, van der Waals interaction or dipole interaction between said second chemical moiety and one of said amino acid residues compared to said first chemical moiety.

57.   (Withdrawn) The method of Claim 52 wherein said nuclear receptor is selected from the group consisting of estrogen receptors, thyroid receptors, retinoid receptors, glucocorticoid receptors, progestin receptors, mineralocorticoid receptors, androgen receptors, peroxisome receptors and vitamin D receptors.

58.   (Withdrawn) The method of Claim 57 wherein said nuclear receptor is an estrogen receptor.

59.   (Withdrawn) The method of Claim 57 wherein the estrogen receptor is the estrogen receptor α.

60.   (Withdrawn) The method of Claim 59 wherein the ligand is an agonist.

61.   (Withdrawn) The method of Claim 60 wherein the ligand is selected from the group consisting of 17β-estradiol, diethylstilbestrol, moxestrol, mesohexestrol, coumestrol, Δ^9-THC, o,p-DDT, zearalenone and kepone.

62.   (Withdrawn) The method of Claim 61 wherein the ligand is 17β-estradiol, and the first chemical moiety is a free carbon of the A' ring located at a position selected from the group consisting of C6α, C7α, C12α, C15α, C16α and C17α.

63.   (Withdrawn) The method of Claim 59 wherein the ligand is an antagonist.

64.   (Withdrawn) The method of Claim 63 wherein the ligand is selected from the group consisting of ICI 164,384 and EM800.

65.   (Withdrawn) The method of Claim 59 wherein the ligand is a selective estrogen receptor modulator.

66.   (Withdrawn) The method of Claim 65 wherein the ligand is selected from the group consisting of tamoxifen, raloxifene and GW5638.

67.   (Withdrawn) A method of modulating nuclear receptor activity in a mammal by administering to a mammal in need thereof a sufficient amount of a ligand that fits spatially and preferentially into a ligand binding domain of a nuclear receptor of interest, wherein said ligand is designed by a computational method comprising:

        fitting an atomic model of the ligand into an atomic structural model of the ligand
        binding domain of the estrogen receptor, wherein the atomic structural model comprises
        atomic coordinates of helix 12 of the ligand binding domain, and of a coactivator binding
        site, and further comprises atomic coordinates of a coactivator bound to the coactivator
        binding site; and
        carrying out a chemical modification of a first chemical moiety of said ligand that
        interacts with the ligand binding domain, to produce a second chemical moiety.

68.   (Withdrawn) The method of Claim 67 wherein the atomic structural model additionally comprises coordinates of at least one amino acid residue that corresponds to human estrogen

receptor α residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421, Leu428, Gly521, His524, Leu525 and Met528, and wherein said first chemical moiety interacts with at least one of said amino acid residues.

69.   (Withdrawn) The method of Claim 67 wherein said ligand is an antagonist.

70.   (Withdrawn) The method of Claim 67 wherein said ligand is an agonist.

71.   (Withdrawn) The method of Claim 70 further comprising administering a coactivator mimic designed by a computational method that comprises: fitting an atomic model of the mimic into the atomic structural model where at least one amino acid residue of the nuclear receptor coactivator binding site that corresponds to human estrogen receptor α helix 3 residues Leu354, Val355, Met357, Ile358, Ala361 and Lys362, helix 4 residue Phe367, helix 5 residues Gln375, Val376, Leu379 and Glu380, helix 6 residue Trp383, and helix 12 residues Asp538, Leu539, Glu542, Met543 and Leu544, interacts with at least one first chemical moiety of said coactivator mimic; and selecting at least one chemical modification of said first chemical moiety to produce a second chemical moiety that has a structure to either decrease or increase an interaction between said coactivator binding site and said second chemical moiety compared to an interaction between said coactivator binding site and said first chemical moiety.

72.   (Withdrawn) The method of claim 1 wherein the test compound is an antagonist that permits helix 12 to bind to a static region of the coactivator binding site.

73.   (Withdrawn) The method of claim 1 wherein the atomic structural model has coordinates presented in Appendix 1.

74.   (Withdrawn) The method of claim 1 wherein the atomic structural model is of a homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog comprises

a ligand binding domain that has a root mean square deviation of not more than 1.5 Å from the backbone atoms of the amino acid residues of the atomic structural model of Appendix 1.

75.   (Withdrawn) The method of Claim 1 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Ala350, Glu353, Leu387, Leu391, Arg394, and Phe404, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an agonist that interacts with at least one of said amino acid residues.

76.   (Withdrawn) The method of Claim 1 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Gly 521, His524, Leu525, and either residues Met421 and Met528, or residues Met388 and Ile424, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an agonist that interacts with at least one of said amino acid residues.

77.   (Withdrawn) The method of Claim 1 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Thr347, Ala350, Trp383, Leu384, Leu387, and Leu525, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an antagonist that interacts with at least one of said amino acid residues.

78.   (Withdrawn) The method of Claim 1 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Met421, Ile 424, Gly 521, His524, and Leu525, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an antagonist that interacts with at least one of said amino acid residues.

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79. (Withdrawn) The method of claim 1 wherein the atomic structural model is experimentally derived.

80. (Withdrawn) The method of claim 79 wherein the atomic structural model has a resolution of at least 2.03 Å.

81. (Withdrawn) The method of claim 4 wherein the modeling further comprises comparing a second atomic structural model of a portion of the estrogen receptor α ligand binding domain with the atomic structural model, wherein the second atomic structural model comprises atomic coordinates of amino acid residues of helix 12 of the ligand binding domain and of a coactivator binding site, wherein the helix 12 contacts the coactivator binding site, and further comprises atomic coordinates of an antagonist molecule bound to the ligand binding domain.

82. (Withdrawn) The method of claim 81 wherein the second atomic structural model is experimentally derived.

83. (Withdrawn) The method of claim 82 wherein the second atomic structural model has a resolution of at least 1.90 Å.

84. (Withdrawn) The method of claim 81 wherein the second atomic structural model has coordinates presented in Appendix 2.

85. (Withdrawn) The method of claim 81 wherein the second atomic structural model is of a homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å from the backbone atoms of the amino acid residues of the atomic structural model of Appendix 2.

86.   (Withdrawn) The method of Claim 14 wherein the test compound is an antagonist that
permits helix 12 to bind to a static region of the coactivator binding site.

87.   (Withdrawn) The method of claim 14 wherein the atomic structural model has
coordinates presented in Appendix 1.

88.   (Withdrawn) The method of claim 14 wherein the atomic structural model is of a
homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog
comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å
from the backbone atoms of the amino acid residues of the atomic structural model of Appendix
1.

89.   (Withdrawn) The method of Claim 14 wherein the atomic structural model additionally
comprises coordinates of amino acid residues that correspond to human estrogen receptor α
residues Ala350, Glu353, Leu387, Leu391, Arg394, and Phe404, wherein said residues lie on a
surface of a binding pocket in the ligand binding domain, and wherein said test compound is an
agonist that interacts with at least one of said amino acid residues.

90.   (Withdrawn) The method of Claim 14 wherein the atomic structural model additionally
comprises coordinates of amino acid residues that correspond to human estrogen receptor α
residues Met343, Leu346, Gly 521, His524, Leu525, and either residues Met421 and Met528, or
residues Met388 and Ile424, wherein said residues lie on a surface of a binding pocket in the
ligand binding domain, and wherein said test compound is an agonist that interacts with at least
one of said amino acid residues.

91.   (Withdrawn) The method of Claim 14 wherein the atomic structural model additionally
comprises coordinates of amino acid residues that correspond to human estrogen receptor α
residues Met343, Leu346, Thr347, Ala350, Trp383, Leu384, Leu387, and Leu525, wherein said

residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an antagonist that interacts with at least one of said amino acid residues.

92.   (Withdrawn) The method of Claim 14 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Met421, Ile 424, Gly 521, His524, and Leu525, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an antagonist that interacts with at least one of said amino acid residues.

93.   (Withdrawn) The method of Claim 14 wherein the modeling comprises providing the atomic coordinates of the portion of the estrogen receptor α ligand binding domain to a computerized modeling system.

94.   (Withdrawn) The method of claim 14 wherein the atomic structural model is experimentally derived.

95.   (Withdrawn) The method of claim 94 wherein the atomic structural model has a resolution of at least 2.03 Å.

96.   (Withdrawn) The method of Claim 14 wherein the test compound is an antagonist that causes a change in position of helix 12 so that helix 12 contacts the coactivator binding site thereby inhibiting coactivator binding.

97.   (Withdrawn) The method of claim 96 wherein the modeling further comprises comparing a second atomic structural model of a portion of the estrogen receptor α ligand binding domain with the atomic structural model, wherein the second atomic structural model comprises atomic coordinates of amino acid residues of helix 12 of the ligand binding domain and of a coactivator binding site, wherein the helix 12 contacts the coactivator binding site, and further comprises atomic coordinates of an antagonist molecule bound to the ligand binding domain.

98.   (Withdrawn) The method of claim 97 wherein the second atomic structural model is experimentally derived.

99.   (Withdrawn) The method of claim 98 wherein the second atomic structural model has a resolution of at least 1.90 Å.

100.   (Withdrawn) The method of claim 97 wherein the second atomic structural model has coordinates presented in Appendix 2.

101.   (Withdrawn) The method of claim 97 wherein the second atomic structural model is of a homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å from the backbone atoms of the amino acid residues of the atomic structural model of Appendix 2.

102.   (Withdrawn) The method of Claim 24 wherein said screening is in vitro.

103.   (Withdrawn) The method of Claim 102 wherein said screening is high throughput screening.

104.   (Withdrawn) The method of Claim 24 wherein said test compound is from a library of compounds.

105.   (Withdrawn) The method of Claim 24 wherein said test compound facilitates binding of a coactivator to the coactivator binding site.

106.   (Withdrawn) The method of Claim 24 wherein said test compound is a small organic molecule, a peptide, or peptidomimetic.

107.   (Withdrawn) The method of Claim 24 wherein the test compound is an agonist that permits the coactivator molecule to bind to a static region of the coactivator binding site.

108.   (Withdrawn) The method of Claim 24 wherein the modeling comprises providing the atomic coordinates of the portion of the estrogen receptor α ligand binding domain to a computerized modeling system.

109.   (Withdrawn) The method of Claim 24 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Ala350, Glu353, Leu387, Leu391, Arg394, and Phe404, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an agonist that interacts with at least one of said amino acid residues.

110.   (Withdrawn) The method of Claim 24 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Gly 521, His524, Leu525, and either residues Met421 and Met528, or residues Met388 and Ile424, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an agonist that interacts with at least one of said amino acid residues.

111.   (Withdrawn) The method of claim 24 wherein the atomic structural model is experimentally derived.

112.   (Withdrawn) The method of claim 111 wherein the atomic structural model has a resolution of at least 2.03 Å.

113.   (Withdrawn) The method of claim 24 wherein the atomic structural model has coordinates presented in Appendix 1.

114.   (Withdrawn) The method of claim 24 wherein the atomic structural model is of a

homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog

comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å

from the backbone atoms of the amino acid residues of the atomic structural model of Appendix

1.

115.   (Withdrawn) A method for identifying an antagonist of ligand binding to an estrogen

receptor, the method comprising:

    modeling a test compound which fits spatially into an atomic structural model of the

    estrogen receptor α ligand binding domain, wherein the atomic structural model

    comprises atomic coordinates of helix 12 of the ligand binding domain, and atomic

    coordinates of a coactivator binding site, and further comprises atomic coordinates of a

    coactivator bound to the coactivator binding site; and

    screening in an assay for estrogen receptor activity a compound which decreases the

    activity of the estrogen receptor by binding the ligand binding domain of the estrogen

    receptor, thereby identifying an agonist of ligand binding.

116.   (Withdrawn) The method of Claim 115 wherein the atomic structural model additionally

comprises coordinates of amino acid residues that correspond to human estrogen receptor α

residues Met343, Leu346, Ala350, Glu353, Leu384, Leu387, Leu391, Arg394, Phe404, Met421,

Leu428, Gly521, His524, Leu525 and Met528, and wherein said test compound interacts with at

least one of said amino acid residues.

117.   (Withdrawn) The method of Claim 115 wherein said screening is in vitro.

118.   (Withdrawn) The method of Claim 117 wherein said screening is high throughput

screening.

119.   (Withdrawn) The method of Claim 115 wherein said test compound is from a library of compounds.

120.   (Withdrawn) The method of Claim 115 wherein the test compound is an antagonist that causes a change in position of helix 12 so that helix 12 contacts the coactivator binding site thereby inhibiting coactivator binding.

121.   (Withdrawn) The method of Claim 115 wherein the test compound is an antagonist that permits helix 12 to bind to a static region of the coactivator binding site.

122.   (Withdrawn) The method of Claim 115 wherein the modeling comprises providing the atomic coordinates of the portion of the estrogen receptor α ligand binding domain to a computerized modeling system.

123.   (Withdrawn) The method of Claim 115 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Thr347, Ala350, Trp383, Leu384, Leu387, and Leu525, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an antagonist that interacts with at least one of said amino acid residues.

124.   (Withdrawn) The method of Claim 115 wherein the atomic structural model additionally comprises coordinates of amino acid residues that correspond to human estrogen receptor α residues Met343, Leu346, Met421, Ile 424, Gly 521, His524, and Leu525, wherein said residues lie on a surface of a binding pocket in the ligand binding domain, and wherein said test compound is an antagonist that interacts with at least one of said amino acid residues.

125.   (Withdrawn) The method of claim 115 wherein the atomic structural model is experimentally derived.

126.   (Withdrawn) The method of claim 125 wherein the atomic structural model has a resolution of at least 2.03 Å.

127.   (Withdrawn) The method of claim 115 wherein the atomic structural model has coordinates presented in Appendix 1.

128.   (Withdrawn) The method of claim 115 wherein the atomic structural model is of a homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å from the backbone atoms of the amino acid residues of the atomic structural model of Appendix 1.

129.   (Withdrawn) The method of claim 115 wherein the modeling further comprises comparing a second atomic structural model of a portion of the estrogen receptor α ligand binding domain with the atomic structural model, wherein the second atomic structural model comprises atomic coordinates of amino acid residues of helix 12 of the ligand binding domain and of a coactivator binding site, wherein the helix 12 contacts the coactivator binding site, and further comprises atomic coordinates of an antagonist molecule bound to the ligand binding domain.

130.   (Withdrawn) The method of claim 129 wherein the second atomic structural model is experimentally derived.

131.   (Withdrawn) The method of claim 130 wherein the second atomic structural model has a resolution of at least 1.90 Å.

132.   (Withdrawn) The method of claim 129 wherein the second atomic structural model has coordinates presented in Appendix 2.

133.   (Withdrawn) The method of claim 129 wherein the second atomic structural model is of a

homolog of the portion of the estrogen α receptor ligand binding domain, wherein the homolog

comprises a ligand binding domain that has a root mean square deviation of not more than 1.5 Å

from the backbone atoms of the amino acid residues of the atomic structural model of

Appendix 2.

134.   (Withdrawn) A method of modulating estrogen receptor activity in a mammal by

administering to a mammal in need thereof a sufficient amount of a compound that fits spatially

and preferentially into an atomic structural model of a ligand binding domain of the estrogen

receptor wherein said compound is designed so that binding of a coactivator to a coactivator

binding site on the ligand binding domain is affected.

135.   (Withdrawn) The method of claim 134 wherein said compound is an antagonist and

binding of a coactivator is inhibited.

136.   (Currently amended) An isolated and purified protein complex ~~comprising:~~ consisting of:

an estrogen receptor α ligand binding domain;

an agonist bound to the ligand binding domain of the receptor, wherein the agonist is selected

from the group consisting of: diethylstilbestrol; moxestrol; mesohexestrol; coumestrol; Δ9-THC;

o,p-DDT; zearalenone; and kepone; and

a coactivator bound to a coactivator binding site of the receptor, wherein the coactivator is

GRIP1 or a peptide fragment thereof, wherein the peptide fragment comprises a NR-box amino

acid sequence.

137.   (Currently amended) The isolated and purified protein complex of claim 136, wherein

~~said coactivator is a peptide that~~ the NR-box amino acid sequence comprises a motif whose

sequence is LXXLL (SEQ ID NO: 1), wherein X is any amino acid residue.

138.   (Cancelled)

139.   (Currently amended) An isolated and purified polypeptide consisting of a portion of the human estrogen receptor starting at amino acid residue 305 and ending at amino acid residue 549, as set forth in SEQ ID NO: 27 or SEQ ID NO: 28, bound to a ligand, and bound to a coactivator, wherein the ligand is selected from the group consisting of: diethylstilbestrol; moxestrol; mesohexestrol; coumestrol; Δ9-THC; o,p-DDT; zearalenone; and kepone; and wherein the coactivator is GRIP1 or a peptide fragment thereof, wherein said peptide fragment comprises a NR-box amino acid sequence peptide.

140.   (Withdrawn) A method of identifying a compound that modulates nuclear receptor activity, the method comprising:

> screening a test compound in an assay characterized by binding of a test compound to the ligand binding domain of the nuclear receptor, wherein the test compound has been modeled by spatially fitting an atomic model of the test compound into an atomic structural model of a portion of the estrogen receptor ligand binding domain, wherein said atomic structural model comprises atomic coordinates of amino acid residues of the estrogen receptor coactivator binding site and coordinates of a molecule bound to the coactivator binding site, thereby identifying a test compound that modulates nuclear receptor activity.

141.   (Withdrawn) A method of identifying a compound that modulates estrogen receptor activity, the method comprising:

> screening a test compound in an assay characterized by binding of a test compound to the ligand binding domain of the estrogen receptor, wherein the test compound has been modeled by spatially fitting an atomic model of the test compound into an atomic structural model of a portion of the estrogen receptor ligand binding domain, wherein said atomic structural model comprises atomic coordinates of amino acid residues of the estrogen receptor coactivator binding site and coordinates of a molecule bound to the coactivator binding site, thereby identifying a test compound that modulates estrogen receptor activity.

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142. (Currently amended) The cocrystal of claim [[47]] 44 wherein the NR-box amino acid sequence molecule is a peptide that comprises a motif whose sequence is LXXLL (SEQ ID NO: 1), wherein X is any amino acid residue.

143. (Cancelled)

144. (Previously presented) The cocrystal of claim 44 wherein the agonist is diethylstilbestrol.

145. (Previously presented) The cocrystal of claim 44 wherein said cocrystal diffracts with a resolution value less than 3.6 Å.

146. (Previously presented) The cocrystal of claim 44 wherein said cocrystal diffracts with a resolution value less than 3.0 Å.

147. (Previously presented) The cocrystal of claim 44 wherein said cocrystal diffracts with a resolution value less than 2.4 Å.

148. (Previously presented) The isolated and purified protein complex of claim 136, wherein said agonist is diethylstilbestrol.

149. (Cancelled)

150. (Currently amended) The cocrystal of claim [[143]] 44 wherein the GRIP1 peptide fragment of GRIP1 is a peptide whose sequence is SEQ ID NO: 4.

151. (Cancelled)

152. (Cancelled)

153.   (Currently amended) The isolated and purified protein complex of claim 136 wherein the coactivator is a GRIP1 peptide fragment whose sequence is SEQ ID NO: 4.

154.   (Cancelled)

155.   (New) The cocrystal of claim 44 having resolved atomic structural coordinates presented in Appendix 1.